

### **REMARKS**

In the Office Action mailed January 26, 2006, Claims 1-4 were rejected under 35 U.S.C. 101. Claims 1-5 were rejected under 35 U.S.C. 112, first paragraph. Claims 1-4 were rejected under 35 U.S.C. 103(a).

#### **Rejection under 35 U.S.C. 101**

In the Office Action mailed January 26, 2006, claims 1-4 were rejected under 35 U.S.C. 101. The Office Action stated the claims encompassed transgenic humans and indicated the insertion of "nonhuman" in the claims would overcome the rejection.

In response, claims 1-4 have been amended to specify "non-human" animals. This amendment is supported by the specification as filed on page 3, line 6. It is believed the rejection is overcome. Reconsideration and withdrawal of the rejection is respectfully requested.

#### **Rejection of claims 1-4 under 35 U.S.C. 112, first paragraph**

In the Office Action mailed January 26, 2006, claims 1-4 were rejected under 35 U.S.C. 112, first paragraph because "the specification, while being enabling for a transgenic nonhuman mammal having a genome comprising a heterologous nucleic acid sequence encoding a growth factor and encoding  $\alpha$ -lactalbumin operably linked to a mammary preferential promoter, . . . does not reasonably provide enablement for transgenic humans or methods using transgenic humans." The Office Action stated the rejection can be overcome by limiting the claims to "nonhuman mammal." Claims 1-4 have been amended to specify "nonhuman mammal". This amendment is supported by the specification on page 4, lines 25-26. This amendment is believed to overcome the rejection.

Rejection of claim 5 under 35 U.S.C. 112, first paragraph

In the Office Action mailed January 26, 2006, claim 5 was rejected under 35 U.S.C. 112, first paragraph "because there is no evidence of record that the disclosed double transgenic sows exhibited an increase in milk volume, although the did demonstrate an increased amount of human IGF-1 in their milk." The Office Action continued: "The theory . . . is the overexpression of a-lactalbumin will result in the production of more lactose. The increase in lactose will increase the osmolarity of the milk causing more water to be transported into milk, thus increasing milk volume. However, the specification offers no evidence to support this theory. The art at the time of filing taught, in transgenic sows expressing bovine a-lactalbumin and human IGF-1, the overall all [sic] concentration of lactose did not change sufficiently to increase milk volume. On day 0 of lactation, sows had 46% greater lactose concentration than nontransgenic sows but by d 5, the difference had disappeared. The end result was no increase in lactalbumin concentration, and, according the theory, without an increase in lactalbumin concentration there would be no increase in milk volume."

It is noted that the claim does not recite any particular theory for increasing the volume of milk, and as such, the theory is not believed to impact the claims and is not discussed further here. The Office Action indicated the claim was enabled as it is directed to an increase in growth factor. Therefore, this response addresses the aspect of the claim directed to increase in volume of milk. In response to the rejection, the claim recites only "a method of increasing the volume of milk"—there is no requirement in the claim that the increase in volume of milk occurs over some specific time period, or that the increase in volume of milk is permanent. The specification provides examples of increasing the volume of milk in transgenic animals having the genome claimed in claim 5 (see specification, page 32, lines 19-20; example 3A (page 40, lines 10-19) and Figure 4 which show higher milk production in transgenic sows relative to control sows). It is believed this description and the results shown in the specification provide evidence of enablement for claim 5.

In addition, applicants provide additional evidence that claim 5 is enabled by the description in the application as filed in Appendix A. Appendix A includes a Declaration by two of the inventors, as well as two Figures. In Figure 1, offspring of transgenic sows, including those expressing both a growth factor gene and alpha-lactalbumin made as described in the specification (designated as  $\alpha$ -Lac/IGF-I in Figure 1) show an increase in milk volume as compared to control (nontransgenic sows). The milk volume is approximately steady in the transgenic sows after day 3. The control sows show a lower milk volume than the transgenic sows at early time points and then the milk production of control sows increases. The increase in control (nontransgenic sows) from day 3 to day 15 is due to a physiologic effect: the piglets are consuming all the milk produced by the mother, so the mother produces more milk. This effect is well known in the art. In Figure 1, the milk production of transgenic sows levels off because of another well-known physiologic effect: the young piglets are too small to consume all the milk the transgenic sow is producing, so the sow does not continue to increase the production of milk. This effect is further illustrated in Figure 2, where transgenic sows expressing a-lactalbumin (bALA) show an 31% increase in milk yield in response to increased nursing stimulation as compared to control (non-transgenic animals) which show a 4% increase in milk yield in response to increased nursing stimulation. Therefore, even when the nursing is stimulated beyond what the nursing piglets provide, there is a significant difference in the milk volume between the transgenic sows and the control sows.

The data present in the application, as well as the additional information presented in Appendix A, prove that claim 5 is enabled by the description in the specification as filed.

New claim 6 has been added which is directed to a method of increasing the growth factor content of milk, which method was said to be enabled in the Office Action.

Rejection under 35 U.S.C. 103(a)

In the Office Action mailed January 26, 2006, claims 1-4 were rejected under 35 U.S.C. 103(a) over Bleck (1998) J. Animal Sci. 76, 3071-3078 (Bleck-a) and Bleck (1998) F. Animal Sci. 76, Suppl. 1/J. Dairy Sci., Suppl. 1., page 213, abst 828 (Bleck-b). The Office Action stated:

Bleck-a teaches the production of transgenic pigs whose genome comprise bovine a-lactalbumin genomic sequence including the endogenous expression regulatory sequences and coding sequences operably linked to a DNA sequence encoding. Bleck-a offers motivation in stating that pigs expressing bovine a-lactalbumin began producing the protein in their milk at d 0 of lactation, whereas pigs begin expressing the endogenous pig a-lactalbumin later. Thus the transgenic pigs expressed elevated levels of a-lactalbumin. Bleck-a offers motivation in stating that the milk produced by these pigs contained a greater amount lactose, leading to faster growth a piglets, a desired effect for increasing the number of piglets born per sow per year.

Bleck-b teaches transgenic pigs whose genome comprise bovine a-lactalbumin expression regulatory sequences operably linked to a DNA sequence encoding human insulin like growth factor I (lines 9-12). Bleck-b further teaches a transgenic boar has been mated and passed the transgene on to three female offspring (lines 14-19). Bleck-b provides motivation in stating that piglets fed insulin like growth factor for the first 13 days post partum had longer intestinal villi and higher lactase activity than piglets fed formula alone (lines 1-4).

In response, a *prima facie* case of obviousness is not made. "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991), cited in MPEP 706.02(j).

To summarize the reference teachings, Bleck-a teaches a transgenic pig containing the  $\alpha$ -lactalbumin gene, where the transgenic pig shows increased  $\alpha$ -lactalbumin in the milk. Bleck-b teaches the production of a transgenic pig having the bovine  $\alpha$ -lactalbumin gene and the gene encoding human IGF-I peptide. However, no results are given pertaining to the characteristics of the transgenic pig in Bleck-b.

Turning to the obviousness issue, first, there is no suggestion or motivation to modify or combine the reference teachings. The Bleck-a reference is directed to production of transgenic pigs expressing  $\alpha$ -lactalbumin in order to analyze the effect of overproduction of this milk protein on the milk production and piglet growth. There is no discussion or mention of IGF-I in the Bleck-a reference, and no suggestion that it might be beneficial to include IGF-I.

Second, there is no reasonable expectation of success of the modification or combination of reference teachings, contrary to the statement in the Office Action: "Some descendents would obviously have the transgenes and demonstrate increased growth factor and  $\alpha$ -lactalbumin in their milk. There was a reasonable expectation of success at the time of filing to achieve this." No support is given for this statement, and in fact, the references themselves show there was no reasonable expectation of success. Bleck-a states "the transgenic animals grew at the same rate as controls, . . . This is different from transgenic pigs that expressed the mouse whey acidic protein gene. In these sows, high production of the transgene resulted in poor lactational performance and agalactia in some animals." (Bleck-a, page 1076, column 1, lines 1-9). This statement in Bleck-a shows that there was uncertainty in the results of producing transgenic animals—some transgenic animals did not have the desired and expected characteristics. In addition, Bleck-b states "our goal was to produce transgenic mice and pigs to analyze the effects that higher mammary and milk levels of insulin-like growth factor I (IGF-I) will have on neonatal growth, intestinal health and piglet survival as well as on sow mammary growth and milk synthesis." This statement

in Bleck-b shows that there was no certain result that was expected from the experiments.

Third, the references when combined do not teach all claim limitations. Neither reference teaches an increased amount of growth factor in the milk of the transgenic animals, a requirement of both independent claims 1 and 4.

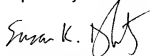
In view of the above arguments, the rejection is believed overcome. Reconsideration and withdrawal of the rejection is respectfully requested.

### CONCLUSION

In view of the above, it is believed the rejections are overcome. Reconsideration and withdrawal of the rejections is respectfully requested. If there are issues remaining to patentability, the Examiner is requested to telephone the undersigned.

It is believed that the fee of \$510.00 for three month extension of time is required and the fee of \$100.00 for one additional independent claim over three. Please deduct the amount due from deposit account 07-1969.

Respectfully submitted,



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